Can we repair the brain in Parkinson's disease?

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Parkinson's disease (PD) is a common disorder that typically presents around the age of 70 years with a tremor, slowness of movement and a shuffling gait along with micrographia and a range of non-motor symptoms. The diagnosis is still made clinically and while this turns out to incorrect in a small minority of cases (e.g. the patient has an essential tremor or Multiple system atrophy), this is very unlikely when the diagnosis is made by a movement disorder specialist coupled to an abnormal DaTSCAN and excellent response to dopaminergic medication. Pathologically the condition is characterised by the development of an alpha synuclein pathology at multiple sites in the CNS as well as the enteric nervous system, where many postulate that the disease may begin.[1] Indeed, there is now an emerging school of thought, with some evidence, that PD may start in the gut and olfactory bulb with the misfolding of endogenous alpha synuclein that then spreads and seeds pathology along defined pathways.[2] This would then explain the Braak staging of PD pathology, which was described at the turn of the century, as well as account for the clinical features seen in prodromal or premotor PD.[3] This new pathogenic basis for PD has now led to trials looking at immune therapies/vaccines designed to reduce this spread of pathology and by so doing slow down disease.[4]

While all this is very exciting, the question arises as to whether other approaches for trying to reverse aspects of the PD disease process still have merit – especially those that seek to repair the nigrostriatal dopaminergic pathway – a pathway that has been known to be a key pathological player in PD since the 1960s. This approach, which began in the 1980s, seeks to either replace the lost dopaminergic pathway through the implantation of dopamine cells or the delivery of growth factors to help maintain those cells/fibres that are struggling in the face of the disease process. Both of these approaches are targeted and only deal with one aspect of the disease and are not, and never were seen, as curative. So where do we stand with respect to this strategy in 2019?

The rationale for trying to repair the nigrostriatal pathway

Clearly the best way to treat PD is to diagnose patients at disease onset (before they clinically present with their motor features) and arrest the pathogenic process. This could be through the above approach or using combinations of agents targeting different aspects of the pathological cascade driving the cellular dysfunction and loss in PD, which could include drug repurposing strategies.[5] While all of this is to be encouraged, we also know that restoring dopamine back to normal in early disease with current oral therapies dramatically improves the patient – almost back to normal in the first few years. Of course, with time these treatments start to fail or create side effects – some of which result from stimulation of more intact dopaminergic networks giving neuropsychiatric problems while others come about through non physiological stimulation of the dopaminergic receiving striatal neurons giving dyskinesias. In addition, the disease progresses and affects many other non dopaminergic pathways. Nevertheless, while one reparative treatment cannot stop or help the latter, restoring the dopaminergic nigrostriatal back to a more normal state would negate the need to use the current drugs in PD and all the problems they bring. As such this strategy has the potential to dramatically alter the natural history of treated PD and in theory could mean that all the treatments we currently use for PD become redundant!

Dopamine cell based therapies for PD

In the early 1980s it was shown that the transplantation of foetal dopamine cells from the developing midbrain could survive in the adult rodent brain and restore the animals behaviour largely back to normal when it had been lesioned along the nigrostriatal pathway.[6] This work led by Anders Björklund and colleagues in Lund, Sweden laid the foundation for clinical trials using human foetal ventral mesencephalon (hfVM) at this site led by Olle Lindvall. The first patients in receipt of such tissue did not benefit, but through an iterative process, it was shown to work well in some patients – and more recently this has been extended to show that these grafted cells could survive for up to 24 years with clinical benefits to match.[7] However not all patients improved and even at this time there were concerns about whether this therapy could ever really become a mainline approach in PD given the ethical and practical problems of obtaining such tissue and the inability to standardise it across patients. As a result other cell sources were sought at this time, including adrenal medulla, carotid body, porcine fVM and even engineered retinal pigmentary epithelial cells (Spheramine®), all of which went to clinical trials with no strong signal of efficacy or survival.[8]

However, based on the encouraging results from the Swedish studies using hfVM, other centres took on trialling this therapy and in the 1990s, two NIH funded trials started following the lifting of a federal funding ban on the use of foetal tissue in the USA by President Clinton. These trials were very different in terms of their trial design and execution but both failed to reach their primary end points.[9,10] Following the publication of these trial results in 2001 and 2003 many felt that this marked the end of this cellular reparative approach, while others sought more to reconcile this data with the long term benefits in some of the patients treated in the open label studies.[6] This led to a new EU funded trial, TransEuro, that started in 2010 and which grafted 11 patients between 2015-2018 in the UK and Sweden with a primary end point in 2021 (https://clinicaltrials.gov/ct2/show/NCT01898390).

However, this new trial, while helping to re-establish cellular approaches to PD, still does not get around the ethical and logistical problems of using human foetal tissue. However, this has changed with the development of human embryonic stem and induced

pluripotent stem (iPS) cells and the discovery by Lorenz Studer and Malin Parmar of how to turn such cells into authentic human midbrain neurons.[11,12] This ability to make dopamine cells from such cells has now evolved to the point of clinical trials. The first patient with PD to receive an iPSC derived dopamine cell was reported in November 2018 and other groups and companies are now on the cusp of such trials[13] (https://www.japantimes.co.jp/news/2018/11/09/national/science-health/kyoto-university-performs-worlds-first-ips-cell-transplant-parkinsons/#.XIA2CPZ2u3A).

Even so, the field is still not without risks and controversies including the use of stem cell derived dopamine cells by companies where the pre-clinical data is less convincing.[14] Nevertheless, over the last two years investment in excess of a billion dollars has now gone into this therapeutic approach for PD.

Growth factor based approaches for treating PD

An alternative approach is to try and rescue the remaining dopamine cells/fibres using growth or neurotrophic factors. This has been done around GDNF and the related neurturin using either direct infusions or gene therapies, again with mixed results.

The discovery of GDNF in 1993 and its trophism for dopaminergic midbrain neurons led to the first trial of this agent in the late 1990s when it was directly injected into the cerebral ventricles. This showed no benefits almost certainly because it was unable to get into the brain parenchyma and simply remained in the CSF compartment.[15]

In the early part of this century therefore two groups, one in Bristol led by Steve Gill and the other in Kentucky led by John Slevin sought to directly infuse GDNF into the site of dopamine fibre loss, the striatum, in patients with PD. Both reported success in small numbers of patients,[16,17] which then led to a double blind placebo controlled trial that failed to show any benefits.[18] The reasons for this have been extensively debated and may have included the dose given; the mode of delivery and patient selection. Subsequently this therapy has been trialled again using a new delivery system in Bristol and the results of this trial have just been published.[19,20] The double blind study showed no clinical benefits despite changes on F-dopa scanning while the open label extension phase looked more promising. The reasons as to why this new trial failed will be the subject of further debate, but again patient selection may have been a reason.

The basis for this conclusion comes in part from the work by Ceregene using the GDNF like gene therapy Neurturin. This agent again showed promise in open label studies only to fail in two double blind placebo controlled trials.[21,22] However, pathologically it was shown that in this trial the volume of distribution of the gene therapy was limited and importantly that patients with earlier stage disease had better responses.[23] This would fit with emerging pathological data showing that in the striatum of patients with advancing PD, the number of surviving dopaminergic fibres rapidly declines after about three to five years of motor disease.[24] Furthermore, it has also been shown that alpha synuclein pathology can interfere with the GDNF receptor signalling pathway and that this can be restored through a Nurr 1 pathway[25] – all of which suggests that it may be better to use a dual agent approach in any future trial with GDNF.

In summary, it is still unclear what all this means for future trials of GDNF, although there is still one ongoing in the USA using a gene therapy approach (https://clinicaltrials.gov/ct2/show/NCT01621581). However, it would seem that this agent can have some effect in some PD patients with evidence of target engagement on PET scanning and as such may merit further trials in early stage or even de novo patients.

Conclusion

Strategies to repair the nigrostriatal dopaminergic problems in the PD brain have attracted clinical attention for over 30 years with mixed success. This is in contrast to neuromodulatory approaches using deep brain stimulation and enteral continuous dopamine therapies which have largely shown to work albeit with some complications and limitations.[26] Nevertheless, the logic for what is being pursed with dopamine cell replacement is obvious and has largely failed because of problems of finding reliable cell sources and standardisation of delivery of those cells. This is about to change with the arrival of human pluripotent stem cell therapies, and as such this field will survive or sink in the next five to ten years. As for growth factors for rescuing the dopaminergic network, this has met with less success and the recent trial from Bristol further dampens the reality of this approach, although there may be good reasons as to why this trial failed. However, whether this will lead to a new trial will prove challenging given the many other new approaches that are now been trialled that are designed to target the disease process itself.

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